Synthesis of Thioxoquinazolin-4(3H)-one Derivatives Under Microwave and Ultrasonic Irradiation with Classical Heating

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A series of thioxoquinazolin-4(3H)-one derivatives have been synthesized from hydrazide derivatives **1a-f** using different electrophilic reagent, *e.g.*, aryl isothiocyanate derivatives, carbon disulfide and aromatic aldehydes through nucleophilic substitution, condensation and cyclization reactions. Different methods were used to prepare compounds **2-6**, including microwave irradiation, ultrasonic and classical heating. The compounds were characterized using various spectroscopic techniques. The synthesized compounds exhibited antibacterial activity.

Key Words: Thioxoquinazolin-4(3H)-one, Sonication, Microwave.

INTRODUCTION

Quinazolinone derivatives have been reported to show a variety of biological properties, such as antimicrobial¹⁻⁶, anti-convulsant⁷⁻¹⁰, antitumor¹¹⁻¹⁶, anticoccidial¹⁷, antidepressant¹⁸, antihistaminic^{19,20}, antiinflammatory²¹⁻²⁴ and antiviral^{25,26} activities. Febrifugine and its analogue have been used as an anti malarial treatment²⁷⁻²⁹. In addition, many thioxoquinazolin-4(3H)-one derivatives exhibit a considerable variety of activities, such as anticonvulsant³⁰, anticancer^{31,32}, antiulcer³³ and antiinflammatory and have been used as therapeutic agents for neuro-protection³⁴. Some novel thioxoquinazolinone derivatives have been synthesized using three different methods *i.e.*, conventional synthesis, ultrasonic and microwave irradiation. The structures of these compounds were firmly established by well-defined IR, ¹H NMR, ¹³C NMR, 2D NMR and ESI-MS spectroscopies. These compounds were then examined for antibacterial properties.

EXPERIMENTAL

The melting points (m.p.) were determined using an Electro-thermal IA900 digital capillary melting point apparatus. The IR spectra were recorded in KBr discs on a Perkin Elmer 1000 FT-IR spectrophotometer ($\nu_{\max}$ in cm^{-1}). The ¹H NMR, ¹³C NMR spectra and 2D NMR spectra were collected in DMSO-*d*₆ or (CDCl₃) using a JEOL-ECP-400 and on Bruker 600 MHz spectrometer. The chemical shifts were reported as parts per million (δ ppm) and the coupling constants (*J*) are given in Hz,

tetramethyl silane (TMS) was used as an internal standard. The mass spectra (*m/z*, %) were obtained on an electro spray ionization (positive mode) LCMS, LCMS-MS and UPLC-MS/MS. The ultrasonic irradiation was performed in a J.P. Selecta with a frequency of 50/60 Hz and a nominal power of 770 W. The microwave experiments were performed in a 1000 W domestic microwave oven. The purity of all compounds was checked by TLC using glass plates coated with silica gel (G) and chloroform/methanol (9:1) as a solvent system. A UV lamp was used as a developing agent. Column chromatography: silica gel (70-230 mesh, Merck). Spectral data (IR, NMR, ¹H-¹³C-COSY (HETCOR), DEPT 135 and mass spectra) confirmed the structures of the synthesized compounds.

The components were synthesized using three different methods: (A) Conventional synthesis, (B) ultrasonic synthesis and (C) microwave irradiation.

2-([(6- or 7-Substituted-3-(4-substituted phenyl)-4-oxo-3,4-dihydroquinazolin-2-yl) thio]acetyl)-N-(4-substituted phenyl)-hydrazinecarbothioamide (2a-c)

Method A for synthesis of (2a-c): An equimolar amount of compound **1a**, **1b** or **1c** (0.0008 mol) and aryl isothiocyanate derivatives in absolute ethanol (3 mL) comprised the reaction mixture, which was heated under reflux for 1 h. At the end of the reaction (monitored by TLC), the obtained solid was filtered and washed with ethanol. The solid product was pure and did not require recrystallization.

Method B for synthesis of (2a-c): Equimolar amounts of compound **1a**, **1b** or **1e** (0.0008 mol) and aryl isothiocyanate derivatives in absolute ethanol (3 mL) were placed into a 25 mL conical flask, which was then mixed and irradiated in the water bath of an ultrasonic cleaner at 80 °C for 15 min (TLC). The solid product was pure and did not require recrystallization.

Method C for synthesis of (2a-c): A few drops of absolute ethanol were added to an equimolar amount of compound **1a** or **1e** (0.0002 mol) and aryl isothiocyanate derivatives. Then, the reaction mixture was irradiated in a domestic microwave oven for 5 min (TLC) at a power of 300 W. The solid product was pure and did not require recrystallization.

N-Phenyl-2-([3-(4-methylphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]thio)acetyl)hydrazinecarbothioamide (2a): White fine scales, m.p. 218 °C, yield (%) 86^A 72^B 36^C; IR (KBr, $\nu_{\max}$, cm⁻¹): 3317, 3278, 3180 (NH), 1687 (C=O_{lactam}), 1659 (C=O_{amide}), 1464 (C=S); ¹H NMR (DMSO-*d*₆): 2.42 (3H, s, CH₃), 4.01 (2H, s, CH₂-S-), 7.16 (1H, t, ³J = 7.4, H-4'), 7.29-7.41 (8H, m, H-2', 3', 5', 6', 2'', 3'', 5'', 6''), 7.47 (1H, t, ³J = 8.1, H-6), 7.65 (1H, d, ³J = 8.1, H-8), 7.80 (1H, t, ³J = 8.1, H-7), 8.08 (1H, d, ³J = 8.1, H-5), 9.53, 9.74, 10.37 (3H, br, s. NH groups); ¹³C NMR spectral data of **2a** were confirmed by 2D NMR ¹H-¹³C-COSY (HETCOR) and DEPT 135 experiments: 20.9 (CH₃), 35.0 (CH₂), 126.2 (C-6), 126.3 (C-8), 126.6 (C-5), 128.1 (C-4'), 134.9 (C-7), 157.1 (C=O_{lactam}), 160.8 (C-2), 166.9 (C=O_{amide}), 180.7 (C=S), 119.5, 126.1 (2C), 129.1 (2C), 129.2 (2C), 130.1 (2C), 133.1, 138.9, 139.8, 147.1 (*sp*² carbons); MS: *m/z* (%) 476 (13) [M + H]⁺ (C₂₄H₂₁N₅O₂S₂+H), 309 (100) [M+H-C₇H₈N₃S-H], 269 (33) [M+H-C₉H₁₀N₃OS+H], 208 (24) [C₉H₁₀N₃OS]⁺, 190 (9) [208-OH-H].

2-[(7-Chloro-4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)thio]acetyl-N-4-methylhydrazinecarbothioamide (2b): white fine scales, m.p. 205 °C, yield (%) 88^A 54^B, IR (KBr, $\nu_{\max}$, cm⁻¹): 3314, 3209, 3115 (NH), 1701 (C=O_{lactam}), 1660 (C=O_{amide}), 1468 (C=S); ¹H NMR (DMSO-*d*₆): 2.28 (3H, s, CH₃), 3.95 (2H, s, CH₂-S-), 7.09-7.20 (4H, m, H-2', 6', 3'', 5''), 7.48-7.62 (6H, m, H-6, 3', 4', 5', 2'', 6''), 7.76 (1H, s, H-8), 8.06 (1H, d, ³J = 8.8, H-5), 9.44, 9.74, 10.29 (3H, br, s. NH groups); ¹³C NMR: 20.6 (CH₃), 34.9 (CH₂), 118.4, 125.7, 125.9, 126.3 (2C), 128.6 (2C), 129.4 (2C), 129.7 (2C), 130.2, 134.5, 135.5, 136.3, 139.4, 148.1, 158.8 (C=O_{lactam}), 160.1 (C-2), 166.9 (C=O_{amide}), 180.8 (C=S) [one carbon with the baseline] (*sp*² carbons); MS: *m/z* (%) 510 (9) [M + H]⁺ (C₂₄H₂₀³⁵ClN₅O₂S₂+H), 511 (8) [M+2] (C₂₄H₂₀³⁷ClN₅O₂S₂), 329 (100) [M+H-C₈H₁₀N₃S-H], 289 (11) [M+H-C₁₀H₁₂N₃OS+H], 222 (47) [C₁₀H₁₂N₃OS]⁺, 204 (13) [222-OH-H].

2-[(6-Bromo-4-oxo-3-phenyl-3,4-dihydroquinazolin-2-yl)thio]acetyl-N-4-methoxyhydrazinecarbothioamide (2c): White bowder, m.p. 204 °C, yield (%) 99^A 76^B 93^C, IR (KBr, $\nu_{\max}$, cm⁻¹): 3316, 3243, 3147 (NH), 1699 (C=O_{lactam}), 1654 (C=O_{amide}), 1469 (C=S); ¹H NMR (DMSO-*d*₆): 3.74 (3H, s, OCH₃), 3.98 (2H, s, CH₂-S-), 6.87 (2H, d, ³J = 8.8, H-3'', 5'', XX' part of AA'XX' system), 7.18 (2H, d, ³J = 7.7, H-2', 6', AA' part of AA'XX' system), 7.48-7.61 (6H, m, H-8, 3', 4', 5', 2'', 6''), 7.94 (1H, d, ³J = 8.8, H-7), 8.14 (1H, d, ⁴J = 1.8, H-5), 9.38, 9.64, 10.29 (3H, br, s. NH groups); ¹³C NMR: 35.1 (CH₂), 55.3 (OCH₃), 113.4, 118.3, 121.2 (2C), 127.4, 127.7, 128.6, 128.8, 129.4 (2C), 129.8 (2C), 130.3, 131.8 (2C), 135.6, 137.7,

146.2, 157.9 (C=O_{lactam}), 159.7 (C-2), 166.9 (C=O_{amide}), 181.1 (C=S) (*sp*² carbons); MS: *m/z* (%) 570 (9) [M+H]⁺ (C₂₄H₂₀⁷⁹BrN₅O₃S₂+H), 572 (10) [M+2] (C₂₄H₂₀⁸¹BrN₅O₃S₂+H), 373 (99) [M+H-C₈H₁₀N₃OS-H], 333 (11) [M+H-C₁₀H₁₂N₃O₂S+H], 238 (100) [C₁₀H₁₂N₃O₂S]⁺, 220 (25) [238-OH-H].

6-Bromo-3-phenyl-2-[[4-(4-methoxyphenyl)-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)methyl]thio}quinazolin-4(3H)-one (3)

Method A for synthesis of (3): Synthesis was conducted according to the procedures in the literature³⁵⁻³⁷.

Method B for synthesis of (3): A solution of compound **2c** (0.1 g, 0.0002 mol) in a sodium hydroxide solution (4 %) was placed into a 25 mL conical flask, mixed and irradiated in the water bath of an ultrasonic cleaner at 80 °C for 1.5 h. The mixture was cooled, filtered and acidified with hydrochloric acid (37 %) to a pH of 5-7. The resulting solid was filtered, washed with water and recrystallized from ethanol. A yellowish white powder was obtained; m.p. 280 °C, yield (%) 99^A 22^B, IR (KBr, $\nu_{\max}$, cm⁻¹): 3306 (NH), 1659 (C=O), 1249 (C=S); ¹H NMR (CDCl₃:DMSO-*d*₆): 3.88 (2H, s, CH₂-S-), 3.90 (3H, s, OCH₃), 7.11 (1H, d, ³J = 8.4, H-8), (2H, d, ³J = 8.4, H-3', 5', XX' part of AA'XX' system), 7.27 (2H, d, ³J = 7.5, H-3'', 5'', XX' part of AA'XX' system), 7.36 (1H, d, ³J = 8.4, H-7), 7.45 (1H, t, ³J = 8.4, H-4'), 7.52 (2H, d, ³J = 7.5, H-2'', 6'', AA' part of AA'XX' system), 7.69 (2H, d, ³J = 8.4, H-2', 6', AA' part of AA'XX' system), 8.12 (1H, d, ⁴J = 1.8, H-5), 10.87 (1H, br, s, NH); ¹³C NMR spectral data of **3** were confirmed by 2D NMR ¹H-¹³C-COSY (HETCOR) and DEPT 135 experiments: 29.5 (CH₂), 55.5 (OCH₃), 115.2 (C-8), 117.6 (2C-3', 5'), 128.4 (2C-3'', 5''), 128.6 (C-4'), 129.2 (2C-2'', 6''), 130.0 (C-5), 130.2 (C-7), 137 (2C-2', 6'), 161.6 (C=O_{lactam}), 165.4 (C-2), 169.5 (C=S), 116.1, 134.9, 138.8, 140.8, 147.4, 150.5, 160.4 (*sp*² carbons). MS: *m/z* (%) 552 (39) [M+H]⁺ (C₂₄H₁₈⁷⁹BrN₅O₂S₂+H), 553 (8) [M+2] (C₂₄H₁₈⁸¹BrN₅O₂S₂+H), 521 (6) [M+H-OCH₃], 507 (76) [M+H-CS-H], 463 (20) [M+H-NC₆H₅+2H], 445 (9) [M+H-OCH₃C₆H₄].

Synthesis of potassium-2-([6 or 7-substituted 3-(4-substituted phenyl)-4-oxo-3,4-dihydroquinazolin-2-yl]thio)acetyl)hydrazinecarbodithioate (4a-b): Synthesis was conducted according to the procedures in the literature³⁸. Note that **4** was not detected in this reaction pathway.

2-[(4-Amino-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)methyl]thio} 6- or 7-substituted 3-(4-substituted phenyl)-quinazolin-4(3H)-one (5a-b)

Method A for synthesis of (5a-b): A mixture of the potassium salt **4a** or **4b** (0.0002 mol), hydrazine hydrate 99 % (0.3 mL) and water (1 mL) was heated under reflux for 1 h, diluted with (3 mL) cold water, neutralized with hydrochloric acid (37 %) to a pH of 5-7 and then filtered. The solid was washed with water and purified by silica gel column chromatography (70-230 mesh) using chloroform/ethanol (9:1) as the eluent to yield the pure product (**5a-b**).

Method B for synthesis of (5a-b): A suspension of the potassium salt of **4a** or **4b** (0.0006 mol), hydrazine hydrate 99 % (0.3 mL) and water (9 mL) in a 25 mL conical flask was mixed and irradiated in the water bath of an ultrasonic cleaner

at 80 °C for 45 min, diluted with (3 mL) cold water, neutralized with hydrochloric acid (37 %) to a pH of 5-7 and filtered. The solid was washed with water and recrystallized from ethanol (**5b**) or purified by column chromatography using chloroform/ethanol (9:1) as the eluent (**5a-b**).

2-[(4-Amino-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)methyl]thio}-7-chloro-3-(4-methoxyphenyl)quinazolin-4(3H)-one (5a**):** White powder, m.p. 240 °C, yield (%) 56^A 62^B, IR (KBr, $\nu_{\max}$, cm⁻¹): 3349 (NH), 3301, 3181 (NH₂), 1690 (C=O), 1461 (C=S); ¹H NMR (DMSO-*d*₆): 3.84 (1H, s, OCH₃), 3.97 (1H, s, CH₂), 4.31 (2H, br, s, NH₂), 7.11 (2H, d, ³J = 8.8, H-3', 5', XX' part of AA'XX' system), 7.38 (2H, d, ³J = 8.8, H-2', 6', AA' part of AA'XX' system), 7.47-7.61 (2H, m, H-5, 8), 8.06 (1H, dd, ³J = 8.4, ⁴J = 2.6, H-6), 10.31 (1H, br, s, NH); ¹³C NMR: 34.6 (CH₂), 54.7 (OCH₃), 113.9 (2C), 117.6, 124.2, 125.2, 125.3, 128.0, 129.7 (2C), 138.5, 147.3, 150.5, 155.6, 159.5, (C=O_{lactam}), 162.4 (C-2), 167.8 (C=S) (*sp*² carbons).

2-[(4-Amino-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)methyl]thio}-6-bromo-3-(4-methylphenylphenyl)quinazolin-4(3H)-one (5b**):** Pale gray powder, m.p. 195 °C, (from ethanol); yield (%) 50^A, 59^B, IR (KBr, $\nu_{\max}$, cm⁻¹): 3349 (NH), 3301, 3181 (NH₂), 1690 (C=O), 1461 (C=S); ¹H NMR (CDCl₃:DMSO-*d*₆): 2.46 (1H, s, CH₃), 3.82 (1H, s, CH₂), 4.09 (2H, br, s, NH₂), 7.23 (2H, d, ³J = 8.1, H-3', 5', XX' part of AA'XX' system), 7.36 (2H, d, ³J = 8.1, H-2', 6', AA' part of AA'XX' system), 7.56 (1H, d, ³J = 9, H-8), 7.83 (1H, dd, ³J = 9, ⁴J = 2.4, H-7), 8.24 (1H, d, ⁴J = 2.4, H-5), 9.81 (1H, br, s, NH); ¹³C NMR spectral data of **5b** were confirmed by 2D NMR ¹H-¹³C-COSY (HETCOR) and DEPT 135 experiments: 21.2 (CH₃), 34.4 (CH₂), 128.2 (C-8), 128.7 (2C-3', 5'), 129.1 (C-5), 130.2 (2C-2', 6'), 137.5 (C-7), 157.7 (C=O_{lactam}), 160.1 (C-2), 167.4 (C=S), 118.6, 121.1, 132.5, 140.2, 146.2 [one carbon with the baseline] (*sp*² carbons).

2-[(6 or 7-Substituted (4-substituted phenyl)-4-oxo-3,4-dihydroquinazolin-2-yl)thio]-N'-(3,4 substituted benzylidene)-acetohydrazide (6a-d**)**

Method A for synthesis of (6a-c): Equimolar quantities of hydrazide **1b** or **1e** or **1f** and the substitutes aldehydes (0.0002 mol) were refluxed in absolute ethanol for 2 h (TLC), the reactions were filtered and the products were dried and recrystallized from benzene.

Method B for synthesis of (6a,c-d): A solution of the hydrazides **1b**, **1e** or **1g** and the substituted aldehyde (0.0002 mol) in absolute ethanol was irradiated in the water bath of an ultrasonic cleaner for 15-45 min (TLC). The reactions were filtered and the products were dried and recrystallized from benzene.

Method C for synthesis of (6c-d): A few drops of absolute ethanol were added to an equimolar amount of hydrazide **1e** or **1g** and the substituted aldehyde (0.0002 mol). This solution was irradiated in a microwave for 5-15 min (TLC). The solid product was treated with ethanol, filtered, dried and recrystallized from benzene.

2-[(7-Chloro-3-phenyl-4-oxo-3,4-dihydroquinazolin-2-yl)thio]-N'-(3,4-dimethoxybenzylidene)acetohydrazide (6a**):** Beige scales, m.p. 269 °C, yield (%) 83^A, 36^B, IR (KBr, $\nu_{\max}$, cm⁻¹): 3167 (NH), 1678 (C=O_{lactam}), 1656 (C=O_{amide}); MS: m/z (%) 509 (7) [M+H]⁺ (C₂₅H₂₁³⁵ClN₄O₄S+H), 510 (3) [M+2]

(C₂₅H₂₁³⁷ClN₄O₄S), 329 (100) [M+H-C₉H₁₁N₂O₂-H], 301 (5) [329-CO], 180 (4) [M+H-C₁₆H₁₀³⁵ClN₂O₂S+H].

2-[(7-Chloro-3-phenyl-4-oxo-3,4-dihydroquinazolin-2-yl)thio]-N'-(4-nitrobenzylidene)acetohydrazide (6b**):** Yellowish white fine needles, m.p. 240 °C, yield (%) 77^A, IR (KBr, $\nu_{\max}$, cm⁻¹): 3126 (NH), 1689 (C=O_{lactam}), 1666 (C=O_{amide}); ¹H NMR (CDCl₃:DMSO-*d*₆): 4.48 (1H, s, CH₂), 7.38-7.47 (3H, m, H-3', 4', 5'), 7.47 (1H, d, ⁴J = 1.8, H-8), 7.59-7.60 (3H, m, H-6, 2', 6'), 7.92 (2H, d, ³J = 8.4, H-2", 6", XX' part of AA'XX' system), 8.08 (2H, d, ³J = 8.4, H-5), 8.16 (1H, s, =CH), 8.25 (2H, d, ³J = 8.4, H-3", 5", XX' part of AA'XX' system), 11.93 (1H, br, s, NH); ¹³C NMR spectral data of **6b** were confirmed by 2D-NMR ¹H-¹³C-COSY (HETCOR) and DEPT 135 experiments: 34.1 (CH₂), 123.2 (2C-3", 5"), 125.1 (C-8), 125.8 (C-4'), 127.3 (2C-2", 6"), 128.2 (C-5), 128.8 (2C-3', 5'), 129.3 (2C-2', 6'), 129.7 (C-6), 160.1 (C=O_{lactam}), 164.1 (C-2), 168.9 (C=O_{amide}), 117.9, 135.1, 140.1, 145.5, 147.9, 158.3 (*sp*² carbons); MS: m/z (%) 494 (4) [M+H]⁺ (C₂₃H₁₆³⁷ClN₅O₄S+H), 495 (2) [M+2] (C₂₃H₁₆³⁷ClN₅O₄S), 329 (100) [M+H-C₇H₆N₃O₂-H], 301 (10) [329-CO], 128 (3 %) [301-Ph-N=C=O], 166 (4) [M+H-C₁₆H₁₀³⁵ClN₂O₂S+H].

N'-(4-Bromobenzylidene)-2-[(6-bromo-3-phenyl-4-oxo-3,4-dihydroquinazolin-2-yl)thio]acetohydrazide (6c**):** White scales, m.p. 257 °C, yield (%) 99^A, 75^B, 99^C, IR (KBr, $\nu_{\max}$, cm⁻¹): 3180 (NH), 1696 (C=O_{lactam}), 1673 (C=O_{amide}); MS: m/z 571 (7) [M+H]⁺ (C₂₃H₁₆⁷⁹Br₂N₄O₂S+H), 573 (16) [M+2] (C₂₃H₁₆^{79,81}Br₂N₄O₂S+H), 575 (7) [M+4] (C₂₃H₁₆⁸¹BrN₄O₂S+H), 373 (100) [M+H-C₇H₆⁷⁹BrN₂], 345 (15) [373-CO], 210 (13) [M+H-C₉H₈⁷⁹BrN₂O-Ph-N=C=O-2H].

2-[(6-Iodo-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl)thio]-N'-(4-nitrobenzylidene)acetohydrazide (6d**):** White scales, m.p. 264 °C, yield (%) 84^A, 71^B, 99^C, IR (KBr, $\nu_{\max}$, cm⁻¹): 3178 (NH), 1680 (C=O_{lactam}), 1680 (C=O_{amide}); MS: m/z (%) 616 (24) [M+H]⁺ (C₂₄H₁₈IN₅O₅S+H), 451 (100) [M+H-C₇H₆N₃O₂-H], 423 (2) [451-CO].

Antibacterial activity: The *in vitro* antibacterial activity of some compounds was determined using the cup-plate diffusion method³⁹. The nearest zone of inhibition was measured in mm. The concentration (100 µg/mL) of the test compounds was adjusted by dissolving the compounds in dimethyl sulfoxide. The antibiotic gentamycin was used as a standard (100 µg/mL) antibacterial agent. The antibacterial activity was screened against two gram-negative bacteria (*Escherichia coli* ATCC25922 and *Pseudomonas aeruginosa* ATCC27853) and two gram-positive bacteria (*Bacillus subtilis* ATCC6633 and *Staphylococcus aureus* ATCC25923), the bacterial cultures were adjusted to 0.5 McFarland turbidity standard.

RESULTS AND DISCUSSION

The condensation of the hydrazide derivative **1a,b,e** with aryl isothiocyanate derivatives resulted in the formation of **2a-c**. Different methods were used to prepare **2a-c**, in good yield, including the traditional methods, microwave and ultrasound irradiation methodologies. The structures of **2a-c** were assigned on the basis of the spectroscopic analyses. The IR spectrum of compound **2a** exhibited bands at 3317, 3278 and 3180 cm⁻¹ due to NH stretching and the lactam C=O stretching of the quinazolinone ring and amide C=O stretching

were observed at 1686 and 1659 cm^{-1} , respectively. The ^1H NMR spectrum of **2a** exhibited a singlet at δ 2.42 ppm, which corresponded to the methyl protons and a singlet at δ 4.01 ppm, which corresponded to the methylene group. A triplet signal was also observed at δ 7.15 ppm ($J = 7.4$ Hz), which was assigned to H-4'. This spectrum also displayed a multiplet signal at δ 7.29-7.41 ppm, which integrated to eight protons and was assigned to protons C-2', 3', 5', 6', 2'', 3'', 5'' and 6-H, whereas the doublet signal at δ 7.47 ppm ($J = 8.1$ Hz) was assigned to H-6. Two doublet signals were observed at δ 7.65 ppm and δ 8.08 ppm ($J = 8.1$ Hz), which were assigned to the protons at positions 8 and 5, respectively (**Scheme-I**) and the doublet signal at δ 7.80 ppm ($J = 8.1$ Hz) was assigned to H-7. Furthermore, the presence of singlet signals at δ 9.53, 9.74 and 10.34 ppm, which are exchangeable with D_2O , were assigned to the NH groups. The ^{13}C NMR spectrum of **2a** displayed signals at δ 20.9 ppm for the methyl carbon, 35.0 ppm for the methylene group carbon, 126.2 ppm for C-6, 126.3 ppm for C-8, 126.6 ppm for C-5, 134.9 ppm for C-7, 128.3 ppm for C-4'', 157.1 ppm for (C=O lactam), 160.8 ppm for C-2, 166.9 ppm for (C=O amide), 180.7 ppm for (C=S) and 9 lines at δ 119.5, 133.1, 138.9, 139.8, 147.1, 126.1 (2C), 129.1 (2C), 129.2 (2C), 130.1 (2C) for other aromatic carbons. The assignment of all protons and carbons in **2a** were verified by the analysis with DEPT and ^1H - ^{13}C Cosy techniques. The mass spectrum of **2a** exhibited a molecular ion peak $[\text{M}+\text{H}]^+$ at m/z 476 which is in agreement with its assigned structure.

Compound **2c** was used in the cyclization reaction with sodium hydroxide under reflux and produced the triazothione **3**, which was also obtained following ultrasound irradiation under the same conditions in moderate yield. The IR spectrum of **3** exhibited an absorption band at 3306 cm^{-1} for NH group, the strong absorption at 1659 cm^{-1} is due to the (C=O lactam) stretching vibration and the absorption with strong intensity at 1249 cm^{-1} corresponds to a C=S stretching vibration.

The ^1H NMR spectrum of **3** revealed two singlet signals in the aliphatic region at δ 3.88 and δ 3.90, which were integrated for 2 and 3 protons, respectively and attributed to the CH_2 and OCH_3 groups. All other aromatic protons in this spectrum appeared at their expected chemical shifts. The ^{13}C NMR data of **3** were fully consistent with its structure. The ^{13}C chemical shift values of some carbons assigned by the 2D NMR ^1H - ^{13}C -COSY(HETCOR) and DEPT 135 data are shown in Fig. 1. The mass spectrum of **3** revealed $[\text{M}+\text{H}]^+$ at m/z 552 and at m/z 553 with almost equal intensity, as expected for bromine isotopes.

The cyclisation of the potassium salts of **4a-b** with 99 % hydrazine hydrate, either using the conventional method or by ultrasoincation, under the conditions stated in (**Scheme-I**) produced the S-triazoles **5a-b** in good-moderate yields. The IR spectrum of compound **5b** exhibited absorption bands at 3241, 3263 and 3202 cm^{-1} , which were assignable to NH/ NH_2 , in addition to the presence of a strong absorption band at 1670 cm^{-1} due to a carbonyl group and C=S stretching frequencies at 1466 cm^{-1} . The ^1H NMR in ($\text{DMSO}-d_6:\text{CDCl}_3$) displayed **3** singlet signals at δ 2.46, 3.82 and 9.18 ppm which are characteristic of a methyl group, methylene protons and a NH proton, respectively. Although the signal from the NH_2 group appeared weak, the aromatic protons appeared as a pair of doublets at

Fig. 1. Structure and ^{13}C NMR data of some carbon atoms in **3**

δ 7.23 ppm (H-3', 5') and δ 7.36 ppm (H-2', 6') with $J = 8.1$ Hz and the other aromatic protons in this spectrum appeared at their expected chemical shifts. Further, the ^{13}C NMR data of **5b** is fully consistent with its assigned structure (Fig. 2).

Fig. 2. ^{13}C chemical shift values some of carbons are assigned by ^1H - ^{13}C -COSY and DEPT 135 data of **5b**

The hydrazide derivatives **1b,e-f** easily condensed with aromatic aldehydes such as 4-bromo benzaldehyde, 3,4 dimethoxyl benzaldehyde and 4-nitro benzaldehyde under different reactions conditions, *e.g.*, microwave irradiation, ultrasonication and classical heating, to produce **6a-d** in excellent yields. The IR spectrum of **6b** exhibited absorption band at 3126 cm^{-1} for the NH group, a band at 1689 cm^{-1} due to C=O(lactam) and a band in the 1666 cm^{-1} region from C=O (amide) stretching. The chemical shifts of all the protons absorptions in the ^1H NMR spectrum of **6b** and the carbon signals in the ^{13}C NMR spectrum were fully consistent with its structure. The mass spectrum of compound **6b** revealed a molecular ion peak at $m/z = 494$ ($[\text{M}+\text{H}]^+$, 18 %) and a base peak was observed in the spectrum at $m/z = 329$ (100 %), which is compatible with its molecular formula of $\text{C}_{23}\text{H}_{16}^{35}\text{ClN}_5\text{O}_4+\text{H}$.

Scheme-I: (i) A: Absolute EtOH, reflux, 1 h (**2a-c**); B: US, 15 min (**2a-c**); C: MW, 5 min (**2a,c**). (ii) A: NaOH (4 %), HCl (37 %), reflux, 3 h; B: US, 1.5 h. (iii) KOH/absolute EtOH, CS₂, dry. ether, stirring, 14 h. (iv) A: H₂O, N₂H₄·H₂O 99 %, HCl (37 %), reflux, 1 h; B: US, 45 min. (v) A: absolute EtOH, reflux, 2 h (**6a-d**); B: US, 15-45 min (**6a,c-d**); C: MW, 5-15 min (**6c-d**). (vi) A: acetic anhydride, reflux, 1-6 h (**7a-d**); B: US, 2 h; C: MW, 1 h

Mallikarjuna *et al.*⁴⁰ reported that refluxing a mixture of hydrazones **6a-d** and acetic anhydride afforded the oxadiazole **7a-d**, also we used microwave and ultrasonic irradiation methods, but when performing the same reaction we did not isolate **7a-d**.

Antibacterial activity: The results of the antibacterial activity are shown in (Table-1). Compounds **2a**, **2b**, **2c** and **5b** exhibited good activities against gram-positive bacterial *S. aureus* whereas compounds **3** and **5a** displayed good activity against the gram-negative bacterial *P. aeruginosa*. Compound **6b** also exhibited good activity against the gram-positive bacterial *B. subtilis* whereas all compounds showed good to moderate activity against the gram-negative bacterial *E. coli*. All of the compounds possessed moderate to poor activities compared to gentamycin.

TABLE-1
ANTIBACTERIAL ACTIVITY AT A
CONCENTRATION OF 100 µg/mL

Test organisms compound	Zone of inhibition in diameter (mm)			
	Gram-negative		Gram-positive	
	<i>E. coli</i>	<i>P. aeruginosa</i>	<i>S. aureus</i>	<i>B. subtilis</i>
2a	11	14	15	9
2b	14	13	17	10
2c	14	11	15	11
3	13	16	0	12
5a	11	16	12	9
5b	11	9	15	9
6b	13	0	10	15
Gentamycin	23	36	27	34

*Diameter of well (bore size) = 5 mm.

Conclusion

The syntheses of some new thioxoquinazolin-4(3*H*)-one derivatives using microwave, ultrasonic and classical heating have been described. The structures of compounds **2-6** were confirmed through spectral data (IR, ¹H NMR, ¹³C NMR, 2D NMR and ESI-MS). The results indicated that the compounds exhibited good to poor antibacterial activity.

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